Results:

Osteoid thickness: As shown in the table below, at Month 18, OTh in ALN + CE was significantly different from PBO (p=0.002), ALN (p=0.012), and CE (p<0.001).

Nonparametric Analysis of Osteoid Thickness
(Unit: Micrometers)

Treatment	N	Observed Median	SE (Median)	Range	Comparison Between Treatments		
					ALN	CE	ALN+CE
PBO	8	6.30**	0.43	(4.60, 8.70)	0.192	0.419	0.002
ALN	23	5.20**	0.29	(4.30, 7.50)		0.453	0.012
CE	27	5.60**	0.32	(3.90, 9.00)			<0.001
ALN+CE	34	4.90**	0.16	(3.80, 6.90)			

Within-treatment test of median=0 ***: p≤0.001 **: p≤0.010 *: p≤0.050.
Overall treatment effect p-value: 0.001.
Pooled SD: 0.92.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

The sponsor states that the decrease found in ALN + CE is most likely due to suppression of bone turnover. The reduced Oth suggests that there was no defect in mineralization.

Comment: It is not clear why suppression of bone turnover should result in a diminution in the thickness of osteoid seams. However, the reductions in Oth in the treatment groups are in keeping with the order of reduction in markers of bone turnover. The data certainly suggest that there was no defect in mineralization of osteoid in association with active treatment and especially with ALN + CE.

Mineral apposition rate (MAR):

As shown in the following table, there was no between-group difference in MAR.

Analysis of Mineral Apposition Rate
(Unit: Micrometers/Day)

Treatment	N	Observed Mean	SD	Adjusted Mean	95% CI	Comparison Between Treatments		
						PBO	ALN	CE
PBO	8	0.55**	0.10	0.52	(0.42, 0.63)	–	–	–
ALN	17	0.54**	0.17	0.51	(0.44, 0.59)		–	–
CE	25	0.52**	0.15	0.49	(0.41, 0.57)			–
ALN+CE	12	0.46**	0.21	0.44	(0.36, 0.51)			

Within-treatment test of mean=0 ***: p≤0.001 **: p≤0.010 *: p≤0.050.
Overall treatment-effect p-value: 0.566.
Pooled SD: 0.16.
Note: Pairwise comparisons were not performed since the overall treatment effect was not significant.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

Comments: Note that patients who had no detectable mineralizing surface (i.e., no tetracycline labeling in the specimen) could not be included in the analysis of MAR. The following (reviewer's) table lists the numbers of patients included in each analysis, by treatment group. The greatest number of patients excluded from the MAR analysis were in the ALN + CE group.

TREATMENT GROUP	# IN OTh ANALYSIS	# IN MAR ANALYSIS
PBO	8	8
ALN	23	17
CE	27	25
ALN + CE	34	12

Osteoid Volume (OV/BV, osteoid volume as a fraction or % of bone volume):

OV/BV differed significantly among the 4 groups, as shown in the following table:

Nonparametric Analysis of Osteoid Volume/Bone Volume
(Unit: Percent)

Treatment	N	Observed Median	SE (Median)	Range	Comparison Between Treatments		
					ALN	CE	ALN+CE
PBO	8	2.11**	0.39	(0.69, 4.17)	0.002	0.023	<0.001
ALN	23	0.58**	0.13	(0.01, 4.03)		0.175	0.057
CE	27	0.62**	0.20	(0.06, 4.34)			<0.001
ALN+CE	34	0.24**	0.08	(0.01, 1.80)			

Within-treatment test of median=0 ***: p≤0.001 **: p≤0.010 *: p≤0.050.
Overall treatment effect p-value: <0.001.
Pooled SD: 0.87.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

The data show a decrease in OV/BV in all active-treatment groups, relative to PBO, and are consistent with suppression of bone turnover in these groups, most prominently in ALN + CE. Again, there is no indication of impaired mineralization.

Mineralizing Surface:

At Month 18, MS differed significantly among the 4 treatment groups, as shown in the table below. Based on the values for MS, ALN + CE had the lowest rate of bone turnover of all 4 treatment groups.

Nonparametric Analysis of Mineralizing Surface
(Unit: Percent)

Treatment	N	Observed Median	SE (Median)	Range	Comparison Between Treatments		
					ALN	CE	ALN+CE
PBO	8	5.14**	1.04	(2.70, 7.17)	<0.001	0.007	<0.001
ALN	23	0.30**	0.14	(0.00, 3.59)	–	<0.001	0.040
CE	27	1.24**	0.49	(0.00, 9.57)	–	–	<0.001
ALN+CE	34	0.09**	0.09	(0.00, 1.02)	–	–	–

Within-treatment test of median=0 ***: p≤0.001 **: p≤0.010 *: p≤0.050.
Overall treatment effect p-value: <0.001.
Pooled SD: 0.69.
PBO: Placebo.
ALN: Alendronate 10 mg.
CE: Conjugated estrogens 0.625 mg.

Taking the mean values (mean data presented elsewhere in NDA), the reductions seen in ALN alone, about 88% lower than PBO, are consistent with earlier data on alendronate. Of note, ALN + CE suppressed the mean values even further, to 95% of PBO.

Comments: Relative to PBO, the median values were suppressed by about 96 and 98% in the ALN and ALN + CE, respectively. The PBO group is postmenopausal and not on HRT. The CE group presumably is estrogen-

sufficient, as judged by degree of suppression of biochemical turnover markers. Relative to this group, the MS/BS in ALN was suppressed by about 75%, and in ALN + CE, the MS/BS was suppressed by about 93%. According to the sponsor, the data show that, in ALN + CE, bone turnover was not "completely" suppressed. However, the level of suppression found in ALN + CE, relative to PBO and even in relation to CE, was nearly 100%. According to the sponsor, 19 individuals had a MS of 0. Fourteen of these were in the ALN + CE group, 4 in ALN, and 1 in CE.[4] In addition, CE+ALN was represented by 22 fewer individuals in the MAR analysis than in the osteoid thickness analysis. Presumably, this was due to the lack of tetracycline labeling in these individuals. The reason for the discrepancy in the number of patients missing from these analyses is not given.

This extreme level of suppression of bone turnover found in ALN + CE is of concern, particularly if this regimen is to be used for extended periods (as it most probably will be). The overall effects of long-term local suppression of bone remodeling are not known. However, it is possible that inhibition of bone remodeling may delay fracture healing or even cause malunion. The safety data base provided by this study (400 women over 2 years) is inadequate to address these concerns.

Bone Architecture

According to the sponsor, overall bone architecture was normal. There was no evidence of woven bone, marrow fibrosis, or other structural abnormalities.

Drug-Demographic Interactions

There were no drug-demographic interactions for safety issues. The analysis considered age, race, and renal function (serum creatinine).

[4] Specimens from these individuals were re-examined using a search within multiple additional sections; evidence for tetracycline labeling of cancellous bone was subsequently found in 16 of these individuals.

8.3.3 Summary of efficacy and safety of Trial 072

This was a 2-year study of 425 hysterectomized postmenopausal women with lumbar spine BMD ≤ -2. Subjects were randomized to placebo, CE alone, ALN alone, and ALN + CE. The study demonstrated that, at the lumbar spine and femoral neck, the BMD increases relative to baseline seen in ALN + CE were greater than in ALN or CE alone.

At these sites, the increases from baseline were:

INCREASES FROM BASELINE (%)

TREATMENT GROUP	LUMBAR SPINE	FEMORAL NECK
ALN	6.0	2.9
CE	6.0	2.6
ALN + CE	8.3*	4.2*

* significantly greater than in either treatment group ($p<0.001$ for both comparisons at the lumbar spine and $p=0.022$ vs ALN and $p=0.003$ vs CE at the femoral neck)

Very small changes from baseline were seen in PBO at either site over the 2 years. All 3 active-treatment groups experienced greater BMD increases than were found in PBO.

Other changes:

Total hip and trochanter: ALN + CE had greater increases than CE alone, but not greater than ALN alone. The differences between CE and ALN + CE were about 2%.

Total body BMD: all 3 active-treatment groups produced significant increases from baseline in total body BMD of about 1.33 to 2.5 %. However, there were no significant differences between treatment groups.

ALN did not differ significantly from CE at any site except the trochanter, where the increases were 5.9% CI: [5.3, 6.6]) for ALN vs 4.3%, CI: [3.8, 4.8] for CE.

The differences in mean % BMD increases from baseline, at 5 anatomic sites, associated with 2 years of treatment with combined [ALN + CE] vs CE alone or ALN alone are summarized in the following (reviewer's) table:

SKELETAL SITE	[ALN+CE] vs CE	[ALN+CE] vs ALN
SPINE	2.27%	2.26%
FEMORAL NECK	1.55%	1.3 %
TROCHANTER	2%	0.6%
TOTAL HIP	1.21%	0.67%
TOTAL BODY	NO DIFFERENCE	NO DIFFERENCE

In an analysis of treatment-by-demographic interactions, the sponsor found that the BMD results were all independent of age, race, or prior estrogen usage. The effects on were also independent of baseline BMD and were similar in the subgroup of individuals with a baseline lumbar spine BMD T-score $\leq$ -2.5 SD.

Biochemical markers of bone resorption and formation were also suppressed more with combined ALN + CE treatment, compared to ALN or CE alone. All 3 active treatment groups experienced statistically significant and quite substantial reductions in NTx/Cr and BSAP during the treatment period. In general, treatment with either ALN or CE alone reduced resorption markers from typically elevated post-menopausal levels to those found in premenopausal women. With combined ALN + CE, the levels declined even further, to between –1 and –2 SD of the mean for premenopausal women. For NTx/Cr , these declines were of the order of 60-70% (from PBO). For BSAP, the reductions were of the order of 50-60% of PBO. ALN produced about the same (for BSAP), or slightly greater (NTx), reductions than were found in CE.

Although ALN + CE substantially reduced BSAP and NTx, the means for both parameters were not less than 2 SD below the reference means for premenopausal women. The sponsor's conclusion is that bone turnover was not completely suppressed. While this is true for the entire skeleton, it may not apply to all sites, particularly sites rich in cancellous bone. The discordance between the histomorphometric parameters and the biochemical parameters, discussed below, is suggestive of this.

Height:

Height was reported as a safety parameter. Of interest, the mean height decreased significantly by 2.6 and 2.1 mm in CE and ALN + CE ($p \leq 0.010$), respectively. For PBO and ALN, there was a nonsignificant increase of 1.4 mm and a decrease of 0.9 mm, respectively.

Comments on this issue appear above. There was clearly no beneficial treatment effect on loss of height.

Safety:

Overall, the safety profile of combined ALN + CE was similar to that of either treatment alone, or to placebo. There were no deaths and very few serious AE's. In this study, there was no evidence for an increase in upper GI AE's in alendronate-treated groups.

It should be noted that the absence of measurable increases in upper GI AE's in this and previous controlled alendronate trials is inconsistent with the numerous reports of upper GI AE's, some very serious, found during the post-marketing period. The cause of this discrepancy has not been elucidated, but poor representation of the intended population by the trial population is a likely possibility. This issue has been discussed in detail previously (see review of the 4-year FIT trial, earlier this year).

Treatment with CE alone or in combination with ALN was not unexpectedly associated with weight gain or breast pain.

Fractures: There were very few incident fractures in the trial: 5 (5.4%) of 92 ALN; 8 (5.7%) of 140 ALN + CE; 4 (8%) of 50 PBO and 10 (7%) of 143 CE. Most of these were non-vertebral fractures, mainly foot, ankle, and rib. There were no laboratory safety issues that were associated with the use of ALN + CE for the 2-year period.

Thus, from the standpoint of routine safety monitoring and tolerability, the use of the combination of the two agents had a favorable profile.

Histomorphometry:

In contrast to the overall safety/tolerability results of this trial, portions of the histomorphometry data were not as reassuring and raised questions about the long-term safety of combined therapy.

From the standpoint of normality of the bone, there was no evidence of impairment in mineralization, nor were there any changes in bone

architecture that would raise any concerns. This is similar to earlier results with alendronate alone.

The problem is not with the architecture or with any lack of mineralization, but with the extreme degree to which bone turnover is suppressed in the combined therapy group. According to the sponsor, this suppression is entirely consistent with the known action of the two agents and with the degree of suppression of the biochemical markers. As noted above, the fact that the marker values remained above –2SD of the premenopausal mean, was interpreted by the sponsor as an indication that bone turnover was not completely shut down by treatment.

In further explaining the nearly complete suppression of turnover seen in the histomorphometry, the sponsor states that ALN "decreases the rate of iliac trabecular (cancellous) bone turnover to a greater extent than in the skeleton as a whole. This is due to the fact that ALN localizes preferentially at sites of active bone turnover, especially highly vascularized ones, such as the ilium. Thus, histomorphometric measurements overestimate the effects of ALN on overall bone turnover. Specific biochemical markers, such as NTx, provide better indices for the effects of ALN on overall skeletal turnover than bone biopsies."

To explain the lack of tetracycline label that was seen in 19 individuals (14 of these on combined ALN + CE, 4 on ALN, and 1 on CE), the sponsor states that active, labeled sites may be missed normally and that one would expect an even greater proportion of individuals to lack tetracycline labeling when taking anti-resorptive agents. This is true, but it still fails to address the fact that none of the 8 PBO and only 1 of 27 CE lacked tetraclycline labeling (as opposed to 4 of the 23 ALN and 14 of the 34 ALN + CE).

Comparison of the histomorphometry data with the changes in biochemical markers shows that the relationship between the two is not simple. For the biochemical markers, the order of suppression potency was [ALN + CE] > ALN > CE. However, the differences between the 3 active-treatment groups were not large (e.g., for NTx, about –70%, -61%, and –52%, respectively; for BSAP, -60%, -50%, and –49%). Despite the fact that this hierarchy was maintained in the histomorphometry results, the differences between the groups was much more substantial in this study. For MS/BS (expressed as %), the results were 0.09, 0.30, 1.24, and 5.14% ([ALN + CE], ALN, CE, PBO, respectively). This means that the bone turnover rate in ALN was 25% that of CE; more striking, the turnover rate of [ALN + CE] was 30% that of ALN and 7% that of CE. Thus, the thirteen-fold difference in bone turnover rate in [ALN + CE], relative to CE, that was seen on histomorphometry was accompanied by only a 45% difference in absolute mean NTx and a 25% difference in BSAP. In other words, there was a 4- to 6-fold disproportion

between the two methods, when the methods were used to compare degrees of suppression of bone turnover among treatment groups. The histomorphometry study was performed at 18 months, and there is no indication whether the suppression of local bone turnover will increase or abate with further treatment.

Assuming that the systemic bone turnover markers represent resorption and formation activity of the entire skeleton, then it is quite probable that the iliac crest (the site of the biopsies), composed mainly of cancellous bone, is not representative of the entire skeleton. It is also significant that, in CE+ALN, BMD continued to increase at nearly all measured skeletal sites at 2 years, with no sign of a plateau. According to the sponsor, this selectivity is a likely explanation for the differences in the turnover results, as well as for the severe degree of suppression found in the biopsy specimens. However, there remains the concern that if this degree of suppression can occur at one site, what evidence is there that it cannot occur at another? Why is the iliac crest a valid indicator site for bone architecture, but not for bone turnover?

One can only speculate about the mechanism of synergy between ALN and CE in suppressing bone turnover, at least at selected sites. However, the extreme degree of suppression raises serious concerns about long term safety, concerns that are not allayed by the sponsor's emphasis on the continued presence of biochemical markers.

In the overall summary, the sponsor concludes that *"there is no evidence that the decrease in bone turnover induced by ALN (alone or in combination with CE) is excessive. The decrease in MS seen in ALN-treated patients in this study is consistent with previous studies, in which ALN was shown to decrease fracture risk."*

I cannot agree with this assessment. There is striking evidence that combined therapy can suppress bone turnover very severely at selected sites. This suppression may not be generalized throughout the entire skeleton, as suggested by the persistence of biochemical markers and the rise in BMD at several sites. Nonetheless, complete local inhibition of bone remodeling may result in microfractures or delayed healing of fractures. Although a decreased rate of fractures was observed in the earlier alendronate trials, and although estrogen alone may prevent fractures, this does not mean that the combination of the two agents (with demonstrably additive effects) will have the same bone safety and efficacy. Further investigation will certainly be required to define the relationship of the iliac crest histomorphometry data with bone metabolism at other skeletal sites.

9 and 10 sNDA 20560-018: Overall assessment of efficacy and safety

This submission consisted of three trials. The first (Protocol 080) was a small, 4-month clinical pharmacology study that compared the effects of estrogen + progestin to estrogen alone on biochemical markers of bone turnover. This study essentially reconfirmed earlier observations that addition of MPA to estrogen did not reduce the bone-sparing effects of estrogen alone.

The second trial, Protocol 097, was a one-year study of the effects of adding alendronate to ongoing HRT in osteopenic women (BMD t-score ≤-2.0). The cause of the osteopenia was thought by the sponsor to be a delay prior to initiation of HRT, combined with a plateau in efficacy of HRT. This assumption is reasonable. Efficacy endpoints were BMD and biochemical markers of bone turnover. The study enrolled 428 postmenopausal women (average age 61 years, average time from menopause onset 15 years) who had taken HRT for an average of 9.6 years. The subjects were randomized 1:1 into HRT alone (continued regimen) or HRT + ALN. Patients continued their individual HRT regimens.

Results:

1) BMD: At the 4 skeletal sites (lumbar spine, femoral neck, trochanter, and Ward's triangle) both treatment groups, HRT alone (PBO) and alendronate (10 mg) plus ongoing HRT (ALN), experienced statistically significant increases above baseline in BMD after 6 and 12 months. The single exception to this was trochanter BMD at 12 months in the PBO group. The increases were generally of the order of about 0.5-1% in the PBO group and 1.6-3.7% in the ALN group. A plausible explanation for the increases in BMD over baseline in the PBO group is increased calcium and vitamin D intake.

Comparisons between groups: The BMD increases found in the ALN + HRT group were statistically significantly greater than those in the HRT + PBO group at the lumbar spine and hip trochanter at 6 and 12 months. However, the differences between groups were not significant at the femoral neck and Ward's triangle.

2) Biochemical markers of bone turnover:

For both groups, the baseline median values for BSAP and NTx were similar to values found in premenopausal women, indicating long term effects of HRT, as well as compliance with HRT regimens.

For the HRT alone group, there was no significant change in BSAP or NTx during the 12 months of the study.

For the ALN (HRT + ALN) group, there were statistically significant decreases from baseline in BSAP (by about 21%) and NTx (by about 42%) at 6 and 12 months. At both 6 and 12 months, the means both markers were slightly below the premenopausal means, but were within 1 SD and remained within the normal premenopausal range.

The between-group (ALN vs PBO) differences in levels of both markers were statistically significant at both 6- and 12-month time points.

Thus, the sponsor demonstrated that, over the course of 12 months, the addition of alendronate, 10mg, to an ongoing regimen of HRT, further suppresses biochemical markers of bone turnover and further increases BMD at the spine and trochanter, but not at the femoral neck and Ward's triangle (where the differences between treatment groups were not significant).

Safety: There were no safety issues as a result of this trial. There was no increase in adverse events in general, or in adverse events usually associated with either treatment alone. There appeared to be an increase in foot fractures in the alendronate-treated patients, but the level of documentation for all fractures remains unclear, based on the data presentation. In any case, there was no increase in fractures in the third trial, which was two-years' duration.

The third trial, Protocol 072, was a two-year study of 425 hysterectomized postmenopausal women with lumbar spine BMD T-score $\leq$ -2. Subjects were randomized to PBO, ALN, CE, and CE + ALN. Efficacy was change from baseline BMD at several anatomic sites, and changes biochemical markers of bone turnover. An additional histomorphometry study was performed on a subset of 96 subjects at 18 months of treatment.

This study demonstrated that the combination of ALN + CE produced increases in BMD at the lumber spine and femoral neck that were greater (by about 2%) than those found in CE or ALN alone. At the total hip and trochanter, ALN + CE produced BMD changes that were about 2% greater than with CE alone, but were not significantly greater than with ALN alone. There were no significant differences between the 3 active treatment groups in total body BMD at 24 months.

Biochemical markers of bone formation and resorption were suppressed into the premenopausal range by all 3 active treatments. The suppression was greater with ALN + CE than with either agent alone.

Curiously, subjects in the ALN + CE and CE alone groups lost about 2.5 mm over the two years; both within-group changes were statistically significant from baseline. Neither the PBO nor the ALN alone group had a statistically significant change in mean height over the two years.

There were no safety issues in the study. There was no increase in specific AE's in ALN + CE over those found in any of the other 3 arms.

There was no significant difference in fracture incidence (vertebral, morphometric vertebral, or non-vertebral) among the 4 arms during the course of the study.

The bone histomorphometry study showed profound inhibition of bone turnover in the ALN + CE group. The MS/BS ratio found in this group was about 30% of that seen in the ALN only group and about 7% of that found in CE. Other histomorphometric parameters indicated no mineralization defect in any treatment group. The bone architecture was normal in all treatment groups. The relationships among systemic markers, local histomorphometric changes, and clinically important outcomes are still unclear and remain to be elucidated.

In summary, there were several overall problems with this submission. From the standpoint of physiology, the combination of ALN and CE may have effects on bone that are not entirely predictable on the basis of knowledge of the action of either agent alone. The synergistic effect of the two agents on suppression of bone turnover is a prime example of this. Given the complexity of the entire system and the large size of the population that will inevitably be exposed to ALN + CE, a larger trial, of size and duration sufficient to examine fracture efficacy, would certainly have been more appropriate. In addition, an approach to the potential problems of delayed fracture healing and malunion of fractures would be very helpful.

In this regard, the emphasis placed on surrogate markers, BMD and biochemical turnover indicators, has hindered our ability to determine the true efficacy and safety of a novel drug combination. When surrogates for a disease are allowed to become the disease itself, the analysis of a complicated issue becomes scientifically simplistic and potentially hazardous. The assumption that an increase in BMD is always beneficial, or that an increase in BMD caused by drug A is physiologically the same as an equivalent increase caused by drug B, is scientifically unsound.

In this sNDA submission, the reliance on BMD as a surrogate for a disease, as well as an indicator for an incompletely understood change in bone physiology, has resulted in a study with uncertain conclusions regarding either clinical efficacy or long term bone safety. A few hundred women

have been exposed to a novel drug combination for one to two years. We know that surrogate markers have changed in the anticipated directions and that these changes have been shown to be associated with beneficial effects in previous studies of alendronate alone. We also know that, overall, there were no obvious safety problems, in terms of adverse experiences. However, we know nothing about meaningful clinical benefits associated with combination therapy. The study lacked sufficient statistical power to detect treatment-associated differences in fracture rates, and, in fact, there was not even a meaningful trend in either direction. If anything, combination therapy had an adverse effect on stature: the ALN + CE group lost height, while the placebo group increased stature non-significantly. In addition, a serious safety concern was raised by the histomorphometric data, a concern that was not allayed by the sponsor's explanation of the bone suppression.

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CONCLUSIONS

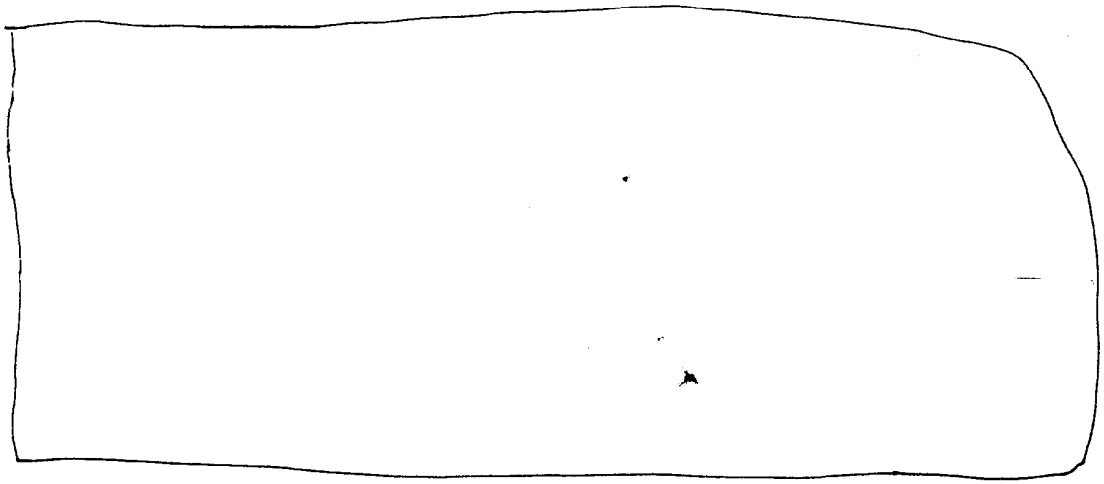
These studies demonstrated that:

1) Over 1 year, alendronate, 10mg/day, added to ongoing HRT, produced greater increases in BMD at selected skeletal sites than were achieved with continuation of HRT alone.
2) In a 2-year study, alendronate plus CE produced greater increases in BMD at selected sites than were achieved with either drug alone.
3) Changes in systemic levels of bone turnover markers were parallel to the BMD changes. The combination ALN + CE produced greater suppression of bone turnover markers than was achieved with either therapy alone.
4) The combination ALN + CE was well tolerated and had an overall safety profile that was essentially the same as that found with either drug alone or with placebo treatment.
5) Histomorphometry data confirmed that bone quality at the iliac crest is architecturally normal following 18 months of treatment with combination therapy. However, at the iliac crest, combined therapy inhibited bone resorption by almost 98%, relative to placebo, and by 70%, relative to alendronate alone. These data raise concerns regarding long-term safety of combination therapy.
6) Fracture efficacy was not part of the study; of some concern, patients on combination therapy lost more height over two years than patients on placebo, with trends towards greater height loss compared to either

group alone. Thus the clinical benefit of combination therapy is not clear, despite changes in surrogate markers.

11 Labeling review

Proposed changes to the current label are presented below. Other, extensive, changes to the Fosamax® label have been negotiated with the sponsor, on the basis of the results of the FIT trial.



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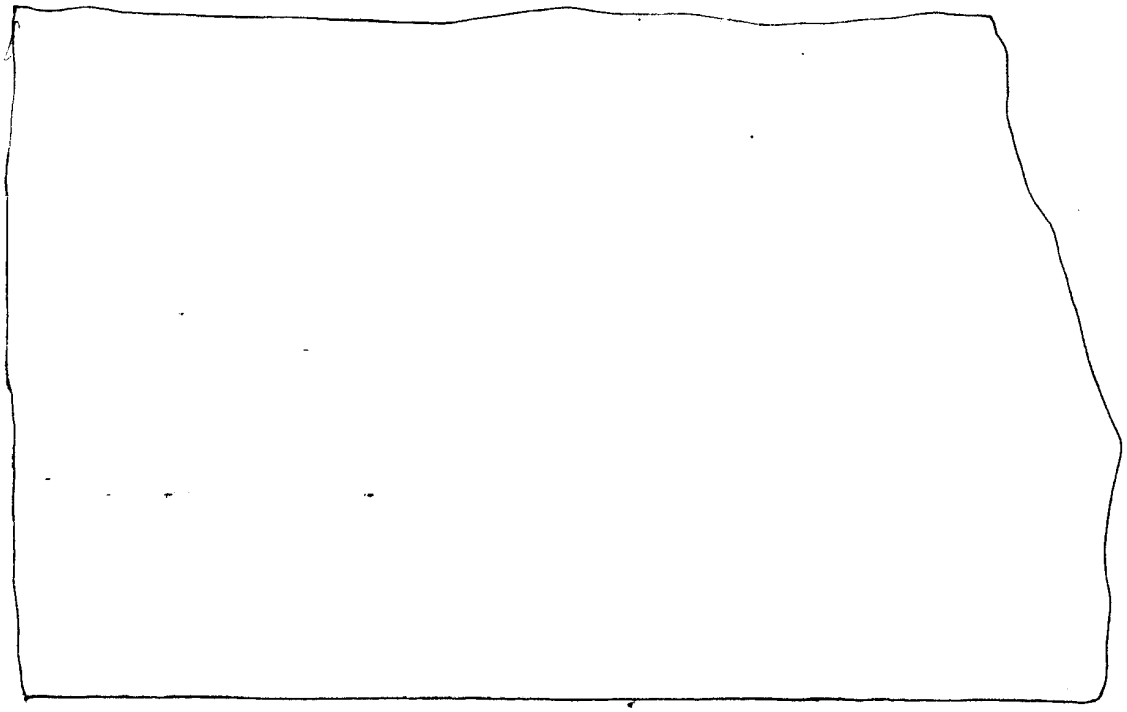
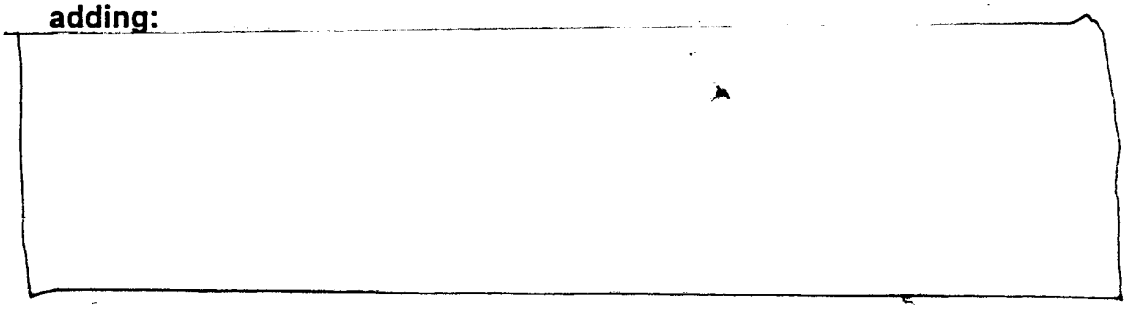
2 pages

DRAFT

LABELING



In the Clinical Pharmacology and Drug Interaction sections, I recommend adding:



RECOMMENDATIONS:

APPROVAL, WITH INDICATED LABELING CHANGES. IT SHOULD ALSO BE MADE CLEAR THAT ALL PROMOTIONAL MATERIAL REGARDING ALENDRONATE WITH HRT MUST CARRY THE ABOVE STATEMENT.

/S/

BRUCE S. SCHNEIDER, MD

/S/ 11/19/99

MEDICAL OFFICER, DMEDP, HFD-510
CC DRS. SOBEL, TROENDLE, MR. HEDIN, HFD-510 FILE

20560n832 November 19, 1999

NDA 20560/S-018
Merck
Alendronate (Fosamax)

Team Leader's Comments on Combined Fosamax and HRT

Safety and efficacy data from 2 trials constitute the principal basis for this NDA supplement.

Another study 080 was a 4-month study of the effect on biochemical markers (Urinary N-Telopeptide/creatinine excretion) of adding progesterone (Medroxyprogesterone acetate, MPA) on days 1-12 of each month to continuous conjugated estrogen (CE). This study in 41 (38 completed) healthy, hysterectomized postmenopausal women, 40-75 yr of age & on HRT at least 1 yr, satisfactorily demonstrated that addition of MPA to ERT did not significantly alter bone markers.

Both Studies 097 and 072 were randomized and placebo-controlled, used 10 mg Alendronate, 0.625 mg CE and compared lumbar spine BMD as the primary endpoint.

Study 097 is a 1 year comparison of effects on BMD induced by Alendronate plus placebo and ALN plus HRT in women who are $\geq$40 years of age, postmenopausal $\geq$5 years (or at least age 25 more and surgically menopausal at least 5 years) with BMD $\leq$2 SD below peak bone mass at the lumbar spine or the femoral neck. 428 participants were enrolled, and 394 completed this study. LS BMD increased more in the ALN plus HRT group than in the placebo plus HRT patients by 2-2.6%.

Study 072 is a 2-year comparison of the effects on BMD of ALN alone compared to CE alone, the combination of ALN and CE, and placebo in 45-75 year old hysterectomized (at least 3 years prior to entry) women who had LS BMD <0.86 g/cm^2. 425 paarticipants were enrolled and 395 completed this study. Results were highly significant increases in BMD (6, 5.99, and 8.265 at the lumbar spine for ALN, CE, and ALN+CE, respectively) with no increase in the placebo patients. This difference is 2.266% more BMD with CE + ALN than with CE alone.

Histomorphometry was done on 92 biopsies on patients in Study 072. This was an important substudy, because the principal concern in combining ALN and HRT in an individual patient has been that we are thus combining two drugs, both of which inhibit bone remodeling. Dr. Schneider's very excellent review addresses the findings in these specimens. Osteoid thickness, mineral apposition rate, osteoid volume, and mineralizing surface were evaluated for signs of bone remodeling or lack of it. In each of the parameters, reduction in patients on CE + ALN exceeded reduction in those on CE alone. Significance of this finding for median OTh, OV/BV, and MS/BS were $P<0.001$, 0.001, and 0.001. For MAR, no significance was found, and observed means were 0.52 and 0.46 for CE and CE + ALN. That is what was intended and expected in combining two agents that both act by inhibiting osteoclasts. The observed median was 0.09 (placebo mean was 5.14), and the range was 0.00 to 1.02 (placebo range was 2.70 to 7.17). This almost total lack of mineralizing surface is frightening.

What happens when bone remodeling is halted completely? Because of the absence of information on this issue, I find it impossible to evaluate this submission as adequate to support the addition of this information to the package insert for Alendronate. If it is to be mentioned in the insert under Clinical Pharmacology, the risks must be stated in language that can be understood by the average or even the below-average physician. The benefits have not been shown to outweigh the risks. I support the wording that was proposed by Dr. Schneider in his review. The designation of histomorphometry results as 98% submission is less acceptable, but may convey the sense we have that further information is necessary. If the sponsor is unable to propose a satisfactory phase study, the application should not be approved.

Recommendations: Approvable if sponsor agrees to do an adequate study post marketing.

/S/ 11/19/99

Gloria Troendle

Cc:HFD-510/NDA 20560

Div File/GTroendle/BSchneider/RHedin/SSobel

November 16, 1999

MEMORANDUM

TO: NDA 20560-S018 FILE

RE: SAFETY UPDATE

A separate safety update has not been included with this submission. However, complete safety data on all patients in the trial were included with the submission, and in my opinion a separate safety update is not needed.

/S/

Bruce S. Schneider, MD

Medical Officer, DMEDP

/S/ 11/16/99

APPEARS THIS WAY
ON ORIGINAL